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EP 0 147 021 B1

Description

This invention relates to a novel composition of use in the treatement of osteitis and osteomyelitis.

In the treatment of osteitis and osteomyelitis, where infection has led to necrosis of bone, it is essential that the necrotic bone (sequester) is removed from the infected site before further treatment can take place. Relatively large cavities are formed in this way and the regeneration of the bone tissue, including the spongeosa, is the primary objective of such further treatment. In our European Patent Application 48558 we have described resorbable gel formulations (which may contain antibacterial substances and other materials which assist bone regeneration and prevent re-infection) to be inserted in granulated form into such cavities to promote tissue growth.

In our above patent application we described gel formulations which contained up to about 20% by weight of calcium phosphate to provide calcium and phosphorus needed for bone formation. However, the granulated gel provided the main bulk of material required to fill the cavity, the voids between the gel granules permitting new tissue to grow into the mass which is gradually resorbed. Eventually, all the gel is resorbed and the cavity is filled by bone tissue. Even calcium phosphate is largely resorbed and regenerated in the physiological form in the new bone.

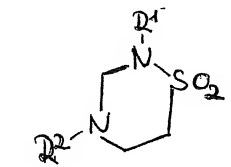
We have now found that an alternative composition for filling into bone cavities resulting from the surgical treatment of osteomyelitis and osteitis comprises an aqueous paste formed from powdered resorbable calcium phosphate and an antibacterial substance resorbable together with one or more binders.

We have further found that the β-tricalcium phosphate is beneficially in substantially pure form in particular being free from the α-form. The purity of the product can be determined by X-ray diffraction; however small quantities up to 2.3% of the α-form may be undetectable.

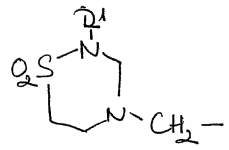
According to the present invention therefore we provide a pharmaceutical composition for filling into bone cavities comprising an aqueous paste containing from 30% to 70% by weight of powdered resorbable substantially pure beta-tricalcium phosphate and an antibacterial substance, together with one or more resorbable binders.

The antibacterial substances employed may be antibiotics and other microbiocidal or microbiostatic substances. In addition, further medicaments, for example analgesic agents may be used. In addition, the compositions can also contain other dissolved additives which promote healing of the wound and/or favourably influence the physical and biochemical properties of the composition. These are, for example, amino acids, sugar, polyhydric alcohols, common salt and others.

When the antibacterial substance is an antibiotic, it is preferably a broad spectrum antibiotic active against both gram-negative and gram-positive bacteria, for example, a β-lactam antibiotic such as a penicillin or cephalosporin, a tetracycline antibiotic, a macrolide antibiotic such as erythromycin, a polypeptide antibiotic such as bacitracin, novobiocin, or, more preferably, an aminoglycoside antibiotic such as streptomycin, neomycin, lincomycin, kanamycin, vancomycin, gentamicin or sisomycin. Typical infecting bacteria include Staphylococcus aureus, Proteus, Pseudomonas, Streptococcus, E. coli, as well as Enterococci, Klebsiella and Staphylococcus albus. However, antibiotics are often contraindicated for use in surgical treatment, due to their tendency to produce resistant strains, and a preferred type of antibacterial substance is a methylol transfer agent, especially noxytiolin or, more preferably taurolidine or a close analogue thereof. Taurolidine is bis-(1,1-dioxo-perhydroxy-1,2,4-thiadiazin-4-yl)methane and this compound and its close analogues can be represented by the formula:



where R^1 is hydrogen or a methyl, ethyl, propyl, butyl or pentyl group and R^2 is hydrogen or a group



where R^1 has the above meaning. Where R^1 and R^2 are both hydrogen, the compound is the methylol transfer antibacterial taurultam.

The preferred active substances are broad spectrum antibiotics and methylol transfer agents such as taurolidine. Taurolidine and its analogues are active against both gram-negative and gram-positive organisms, as well as against the toxins produced by gram-negative bacteria.

The complex of elemental iodine and polyvinyl pyrrolidone may also be advantageously be used as a microbiocidal substance.

It is important that the binder for the calcium phosphate should be resorbable, so that it does not remain and give rise to tissue reactions after the remains of the composition has been resorbed.

In general, polyvinylpyrrolidone can be used as a binder in the formulations. A molecular weight in the range 200-30,000 is preferred. Kollidone 17 (sold by BASF) is one suitable form. Other useful binding agents include gelatin, e.g. edible gelatin, and dextran; the molecular weight of the dextran is preferably about 70,000. The binding agent will commonly comprise 2-10% by weight of the composition e.g. 4-6%.

The compositions of the invention will normally contain a relatively large amount of water, e.g. in the range 30-60%, preferably 40-50%. In general, the proportions of water and binding agent will depend on the consistency which is required. Relatively fluid compositions may be useful in that they can be introduced into the cavity via a post-operative drainage tube. In other instances, however, it may be preferable to pack the cavity with a more solid composition before closing the wound.

The quantity of calcium phosphate in the compositions is, as indicated above, 30% and preferably about 40% by weight; they will normally contain up to 60% or even 70% by weight. This contrasts with the quantities of calcium phosphate incorporated into the gels as described in our above patent application which were always less than 20%.

The quantity of antibacterial substance may conveniently be in the range 0.5-5% by weight. Where taurolidine is used, it is preferably present in the range 1-4% by weight. In large cavities, 2% taurolidine may be sufficient; in small cavities, e.g. in bones in the wrist, 4% by weight of taurolidine is preferred.

The following Examples are given by way of illustration only:-

Example 1	Weight %
β-Tricalcium phosphate (200 microns)	40,00
Taurolidine	4,00
Kollidone 17 PF	5,00
Distilled water	51,00

The above components are blended to give a relatively fluid suspension which can be administered via a drainage tube.

Example 2	Weight %
β-Tricalcium phosphate	50,00
Taurolidine	4,00
Kollidone 17 PF	5,00
Distilled water	41,00

The above components were blended together to yield a thick but still fluid paste which could be administered via a drainage tube and would remain in the cavity.

Example 3	Weight %
β-Tricalcium phosphate	50,00
Taurolidine	4,00
Kollidone 17 PF	5,00
Distilled water	31,00

The above components were blended together to give a moist powder for packing into a bone cavity.

Claims

1. A pharmaceutical composition for filling into bone cavities comprising an aqueous paste containing from 30% to 70% by weight of powdered resorbable substantially pure beta-tricalcium phosphate and an antibacterial substance, together with one or more resorbable binders.

2. A composition as claimed in claim 1 in which the antibacterial substance is taurolidine or taurultam.

3. A composition as claimed in claim 1 or claim 2 which is fluid to enable introduction into said bone cavity via a drainage tube.

4. A composition as claimed in any of claims 1-3 in which polyvinylpyrrolidine, gelatin and/or dextran is present as the resorbable binder.

Revendications

1. Composition pharmaceutique destinée au remplissage de cavités osseuses, comprenant une pâte aqueuse contenant de 30 à 70% en poids d'un phosphatetricalcique-β pulvérulent, pratiquement pur, résorbable et d'une substance antibactérienne, conjointement avec un ou plusieurs liants résorbables.

2. Composition selon la revendication 1, dans laquelle la substance antibactérienne est la taurolidine ou le taurultam.

3. Composition selon la revendication 1 ou la revendication 2, qui est fluide pour permettre son introduction dans ladite cavité osseuse au moyen d'un tube de drainage.

4. Composition selon l'une quelconque des revendications 1 à 3, dans laquelle la polyvinylpyrrolidine, la gélatine et/ou le dextran sont présents en tant que liant résorbable.

Ansprüche

1. Pharmazeutische Zusammensetzung zum Einfüllen in Knochenhöhlen, umfassend eine wäßrige Paste, enthaltend 30 bis 70 Gew.-% gepulvertes resorbierbares, im wesentliches reines β-Tricalciumphosphat und eine antibakterielle Substanz zusammen mit einem oder mehreren resorbierbaren Bindemitteln.

2. Zusammensetzung gemäß Anspruch 1, dadurch gekennzeichnet, daß die antibakterielle Substanz Taurolidin oder Taurultam ist.

3. Zusammensetzung gemäß Anspruch 1 oder Anspruch 2, welche fluid ist, um die Einführung in die Knochenhöhle über eine Drainageröhre zu ermöglichen.

4. Zusammensetzung gemäß einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß Polyvinylpyrrolidon, Gelantine und/oder Dextran als resorbierbares Bindemittel vorhanden ist.